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Biological evaluation of medical devices —

Part 1:
Evaluation and testing within a risk management process

Évaluation biologique des dispositifs médicaux —

Partie 1: Évaluation et essais au sein d'un processus de gestion du risque

Reference number
ISO 10993-1:2018(E)

Contents

Page

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices.*

This fifth edition cancels and replaces the fourth edition (ISO 10993-1:2009), which has been technically revised. It also incorporates the Technical Corrigendum ISO 10993-1:2009/Cor.1:2010.

The main changes compared to the previous edition are as follows:

a) revised Annex A "Endpoints to be addressed in a biological risk assessment" with new columns for "physical and/or chemical information" and "material mediated pyrogenicity" as well as columns for "chronic toxicity," "carcinogenicity," "reproductive/developmental toxicity," and "degradation" which now indicates "endpoints" to be considered with "E" (instead of "tests" to be conducted with an "X");

b) replaced Annex B "Guidance on the risk management process" with "Guidance on the conduct of biological evaluation within a risk management process" (formerly ISO TR 15499);

c) additional definitions for terms used throughout the ISO 10993 series of standards;

d) additional information on the evaluation of "Non-contacting medical devices" and new information on the evaluation of "Transitory-contacting medical devices";

e) additional information on the evaluation of nanomaterials, and absorbable materials;

f) additional reference to ISO 18562 (all parts) for "Biocompatibility evaluation of breathing gas pathways in healthcare applications";

g) significant editing changes throughout the document;

A list of all parts in the ISO 10993 series can be found on the ISO website.

This corrected version of ISO 10993-1:2018 incorporates the following correction.

— In Table A.1, 6th column, “Sensitization” has been added as a table heading.

Introduction

The primary aim of this document is the protection of humans from potential biological risks arising from the use of medical devices. It is compiled from numerous International and national standards and guidelines concerning the biological evaluation of medical devices. It is intended to describe the biological evaluation of medical devices within a risk management process, as part of the overall evaluation and development of each medical device. This approach combines the review and evaluation of existing data from all sources with, where necessary, the selection and application of additional tests, thus enabling a full evaluation to be made of the biological responses to each medical device, relevant to its safety in use. The term “medical device” is wide-ranging and, at one extreme, consists of a single material, which can exist in more than one physical form, and at the other extreme, of a medical device consisting of numerous components made of more than one material.

This document addresses the determination of the biological response to medical devices, mostly in a general way, rather than in a specific device-type situation. Thus, for a complete biological evaluation, it classifies medical devices according to the nature and duration of their anticipated contact with human tissues when in use and indicates, in a matrix, the biological endpoints that are thought to be relevant in the consideration of each medical device category. See also 3.14, Note 1 to entry.

The range of biological hazards is wide and complex. The biological response to a constituent material alone cannot be considered in isolation from the overall medical device design. Thus, in designing a medical device, the choice of the best material with respect to its biocompatibility might result in a less functional medical device, biocompatibility being only one of a number of characteristics to be considered in making that choice. Where a material is intended to interact with tissue in order to perform its function, the biological evaluation needs to address this.

Biological responses that are regarded as adverse, caused by a material in one application, might not be regarded as such in a different situation. Biological testing is based upon, among other things, *in vitro* and *ex vivo* test methods and upon animal models, so that the anticipated behaviour when a medical device is used in humans can be judged only with caution, as it cannot be unequivocally concluded that the same biological response will also occur in this species. In addition, differences in the manner of response to the same material among individuals indicate that some patients can have adverse reactions, even to well-established materials.

The primary role of this document is to serve as a framework in which to plan a biological evaluation. A secondary role is to utilize scientific advances in our understanding of basic mechanisms, to minimize the number and exposure of test animals by giving preference to *in vitro* models and to chemical, physical, morphological, and topographical characterization testing, in situations where these methods yield equally relevant information to that obtained from *in vivo* models.

It is not intended that this document provide a rigid set of test methods, including pass/fail criteria, as this might result in either an unnecessary constraint on the development and use of novel medical devices, or a false sense of security in the general use of medical devices. Where a particular application warrants it, experts in the product or in the area of application concerned can choose to establish specific tests and criteria, described in a product-specific vertical standard.

ISO 10993 series is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcome of the evaluation for each medical device, taking into consideration all the factors relevant to the medical device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience.

Informative Annex A contains a table that is generally helpful in identifying endpoints recommended in the biocompatibility evaluation of medical devices, according to their category of body contact and duration of clinical exposure. Informative Annex B contains guidance for the application of the risk management process to medical devices which encompasses biological evaluation.

Biological evaluation of medical devices —

Part 1: Evaluation and testing within a risk management process

1 Scope

This document specifies:

— the general principles governing the biological evaluation of medical devices within a risk management process;

— the general categorization of medical devices based on the nature and duration of their contact with the body;

— the evaluation of existing relevant data from all sources;

— the identification of gaps in the available data set on the basis of a risk analysis;

— the identification of additional data sets necessary to analyse the biological safety of the medical device;

— the assessment of the biological safety of the medical device.

This document applies to evaluation of materials and medical devices that are expected to have direct or indirect contact with:

— the patient's body during intended use;

— the user's body, if the medical device is intended for protection (e.g., surgical gloves, masks and others).

This document is applicable to biological evaluation of all types of medical devices including active, non-active, implantable and non-implantable medical devices.

This document also gives guidelines for the assessment of biological hazards arising from:

— risks, such as changes to the medical device over time, as a part of the overall biological safety assessment;

— breakage of a medical device or medical device component which exposes body tissue to new or novel materials.

Other parts of ISO 10993 cover specific aspects of biological assessments and related tests. Device-specific or product standards address mechanical testing.

This document excludes hazards related to bacteria, moulds, yeasts, viruses, transmissible spongiform encephalopathy (TSE) agents and other pathogens.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-2:2006, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-3, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization*

ISO 10993-11:2017, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

ISO 10993-16, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

ISO/TS 10993-20, *Biological evaluation of medical devices — Part 20: Principles and methods for immunotoxicology testing of medical devices*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at https://www.iso.org/obp

3.1
biocompatibility
ability of a *medical device* (3.14) or *material* (3.12) to perform with an appropriate host response in a specific application

3.2
biological risk
combination of the probability of harm to health occurring as a result of adverse reactions associated with *medical device* (3.14) or *material* (3.12) interactions, and the severity of that harm

3.3
biological safety
freedom from unacceptable *biological risk* (3.2) in the context of the intended use

3.4
chemical constituent
any synthetic or natural substance that is used in a process for manufacturing *materials* (3.12) and/or *medical devices* (3.14), including the base material(s), additives (antioxidants, UV stabilizers, color additives, dyes, etc.), and processing aids (solvents, lubricants, antifoaming agents, etc.)

3.5
data set
information, such as physical and/or chemical characterization, toxicity data, etc. from a variety of sources necessary to characterize the biological response to a *medical device*

3.6
direct contact
medical device (3.14) or medical device component that comes into physical contact with body tissue

3.7
externally communicating medical device
medical device (3.14) or medical device component that is partially or wholly located outside the body but has either direct or indirect contact with the internal body fluids and/or tissues

3.8
final product
medical device (3.14) or medical device component that has been subjected to all manufacturing processes for the "to be marketed" medical device including packaging and if applicable, sterilization

3.9
geometry
device configuration
shape and relative arrangement of the parts of the *medical device* (3.14)

3.10
implant
medical device (3.14) which is intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye by means of clinical intervention and which is intended to remain in place after the procedure

3.11
indirect contact
medical device (3.14) or medical device component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissue (in this case the medical device or medical device component itself does not physically contact body tissue)

3.12
material
synthetic or natural polymer, metal or alloy, ceramic, or composite, including tissue rendered non-viable, used as a *medical device* (3.14) or any part thereof

3.13
material characterization
broad and general process of collecting existing information about a material's chemistry, structure and other properties, and if appropriate, new data, to facilitate the evaluation of these properties

3.14
medical device
any instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, *material* (3.12) or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

— investigation, replacement, modification, or support of the anatomy or of a physiological process;

— supporting or sustaining life;

— control of conception;

— disinfection of medical devices;

— providing information by means of *in vitro* examination of specimens derived from the human body;

and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means. Medical devices include dental devices.

Note 1 to entry: Products which may be considered to be medical devices in some jurisdictions but not in others include:

— disinfection substances;

— aids for persons with disabilities;

— devices incorporating animal and/or human tissues;

— devices for *in vitro* fertilization or assisted reproduction technologies;

[SOURCE: GHTF/SG1/N071:2012, 5.1 modified to clarify that dental devices are included]

3.15
nanomaterial
material (3.12) with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale

[SOURCE: ISO/TR 10993-22:2017, 3. 7, modified — Notes to entry have been deleted.]

3.16
non-contacting
indicates that the *medical device* (3.14) or medical device component has neither direct nor indirect contact with body tissues

3.17
physical and chemical information
knowledge regarding formulation, manufacturing processes, geometric and physical properties and type of body contact and clinical use that is used to determine whether any additional biological or material characterization testing is needed

3.18
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[SOURCE: ISO 14971:2007, 2.17, modified— The Note has been deleted.]

3.19
risk assessment
overall process comprising a *risk analysis* (3.18) and a *risk evaluation* (3.20)

[SOURCE: ISO 14971:2007, 2.18]

3.20
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO 14971:2007, 2.21]

3.21
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[SOURCE: ISO 14971:2007, 2.22]

3.22
toxic
capable of causing an adverse biological response

3.23
toxicological hazard
potential for a chemical substance or *material* (3.12) to cause an adverse biological reaction, taking into account the nature of the reaction and the dose required to elicit it

3.24
toxicological risk
probability of a specified degree of an adverse reaction occurring in response to a specified level of exposure

3.25
toxicological threshold
limit, such as a tolerable intake (TI), tolerable exposure (TE), allowable limit (AL) value, or Threshold of Toxicological Concern (TTC) below which adverse effects are not expected for relevant biological endpoints

3.26
transitory contact
medical device (3.14) or medical device component that has a very brief duration of contact with body tissue

4 General principles applying to biological evaluation of medical devices

4.1 The biological evaluation of any material or medical device intended for use in humans shall form part of a structured biological evaluation plan within a risk management process in accordance with ISO 14971:2007, Annex I, as given in Figure 1 of this document. This risk management process involves identification of biological hazards, estimation of the associated biological risks, and determination of their acceptability. Annex B provides guidance on this process. The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced professionals.

The risk management plan should identify aspects of the biological evaluation requiring specific technical competencies and shall identify the person(s) responsible for the biological evaluation.

The evaluation shall include documented, informed consideration of advantages/disadvantages and relevance of:

a) medical device configuration (e.g. size, geometry, surface properties) and a listing of a medical device's materials of construction (qualitative) and where necessary, the proportion and amount (mass) of each material in the medical device (quantitative);

b) the physical and chemical characteristics of the various materials of construction and their composition;

NOTE Where this information is already documented within the risk management for the medical device, it can be included by reference.

c) any history of clinical use or human exposure data;

NOTE Previous regulatory approval history can be relevant.

d) any existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites;

e) test procedures.

Evaluation can include both a review of relevant existing preclinical and clinical data and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the medical device under design. The type of information that can be useful to demonstrate equivalence is included in Annex B. Testing is usually not necessary when sufficient information is already available to perform a risk assessment of the material and/or the medical device (see Annex C).

4.2 In the selection of materials to be used in the medical device manufacture, the first consideration shall be fitness for purpose with regard to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties.

4.3 The following shall be taken into account for their relevance to the overall biological evaluation of the medical device:

a) the material(s) of construction (i.e. all direct and indirect tissue contacting materials);

b) intended additives, process contaminants and residues (for example, testing for ethylene oxide sterilization residuals shall be conducted in accordance with ISO 10993-7);

c) packaging materials that directly or indirectly contact the medical device can transfer chemicals to the medical device and then indirectly to the patient or clinician;

d) leachable substances (see ISO 10993-17 and ISO 10993-18);

e) degradation products (see ISO 10993-9, for general principles and 10993-13, 10993-14 and 10993-15 for degradation products from polymers, ceramics and metals, respectively);

f) other components and their interactions in the final product;

g) the performance and characteristics of the final product;

h) physical characteristics of the final product, including but not limited to, porosity, particle size, shape and surface morphology.

Description of medical device chemical constituents and consideration of material characterization including chemical characterization (see ISO 10993-18) shall precede any biological testing (see Figure 1). Chemical characterization with an appropriate toxicological threshold can be used to determine if further testing is needed (see Annex B, ISO 10993-17 and ISO 10993-18).

Physical effects of the medical device shall be considered if they impact the biocompatibility.

NOTE See ISO/TR 10993-19 for information.

Medical devices that contain, generate, or are composed of nanomaterials can pose specific challenges to the biological evaluation due to their potentially unique properties (see ISO/TR 10993-22).

Both local and systemic effects shall be considered for risk evaluation.

4.4 The biological evaluation shall commence with categorization of medical devices (see Clause 6). Assessment of the information already available then enables a gap analysis to facilitate the selection

of appropriate tests. The rigour necessary in the biological evaluation is principally determined by the nature, degree, frequency and duration of the exposure and the hazards identified for the medical device or material. Testing is usually not necessary when sufficient information is already available to perform a risk assessment of the material and/or the medical device (see Annex C). For example, biological testing is usually not necessary, if material characterization (e.g. physical and chemical) demonstrates equivalence to a previously assessed medical device or material with established safety (see ISO 10993-18 and ISO/TR 10993-19).

The interpretation of the data shall take into account the chemical composition of the materials, including the conditions of exposure as well as the nature, degree, frequency and duration of exposure of the body to the medical device or its constituents.

4.5 All known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical (see Clauses 5 and 6). Test results cannot guarantee freedom from potential biological hazards, thus biological investigations shall be followed by careful observations for unexpected adverse reactions or events in humans during clinical use of the medical device.

The range of possible biological hazards is wide and can include short-term effects such as acute toxicity, irritation to the skin, eye and mucosal surfaces, haemolysis and thrombogenicity, as well as long-term or specific toxic effects such as subchronic and chronic toxic effects, sensitization resulting in allergy, genotoxicity, carcinogenicity (tumorigenicity) and effects on reproduction or development, including teratogenicity.

4.6 If testing is needed, selection of any *in vitro* or *in vivo* tests (see Annex A) shall be based on intended use.

In vitro test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible, shall be considered for use in preference to *in vivo* tests (see ISO 10993-2). Whenever *in vivo* tests are indicated by findings of the initial risk assessment, use of appropriate *in vitro* screening, if available, shall be considered before *in vivo* tests are commenced. A rationale for the testing strategy, as well as for test selection, shall be provided. Test data, complete to the extent that an independent analysis could be made, shall be evaluated by competent, informed professionals, and shall be retained.

In certain circumstances, such as for specific medical devices, or biological endpoint assessments, if a non-standardized, non-validated test is necessary, additional information regarding the rationale for the study design and data interpretation should be provided.

4.7 The biological safety of a medical device shall be evaluated by the manufacturer over the whole life-cycle of a medical device.

4.8 For re-usable medical devices, biological safety shall be evaluated for the maximum number of validated processing cycles by the manufacturer.

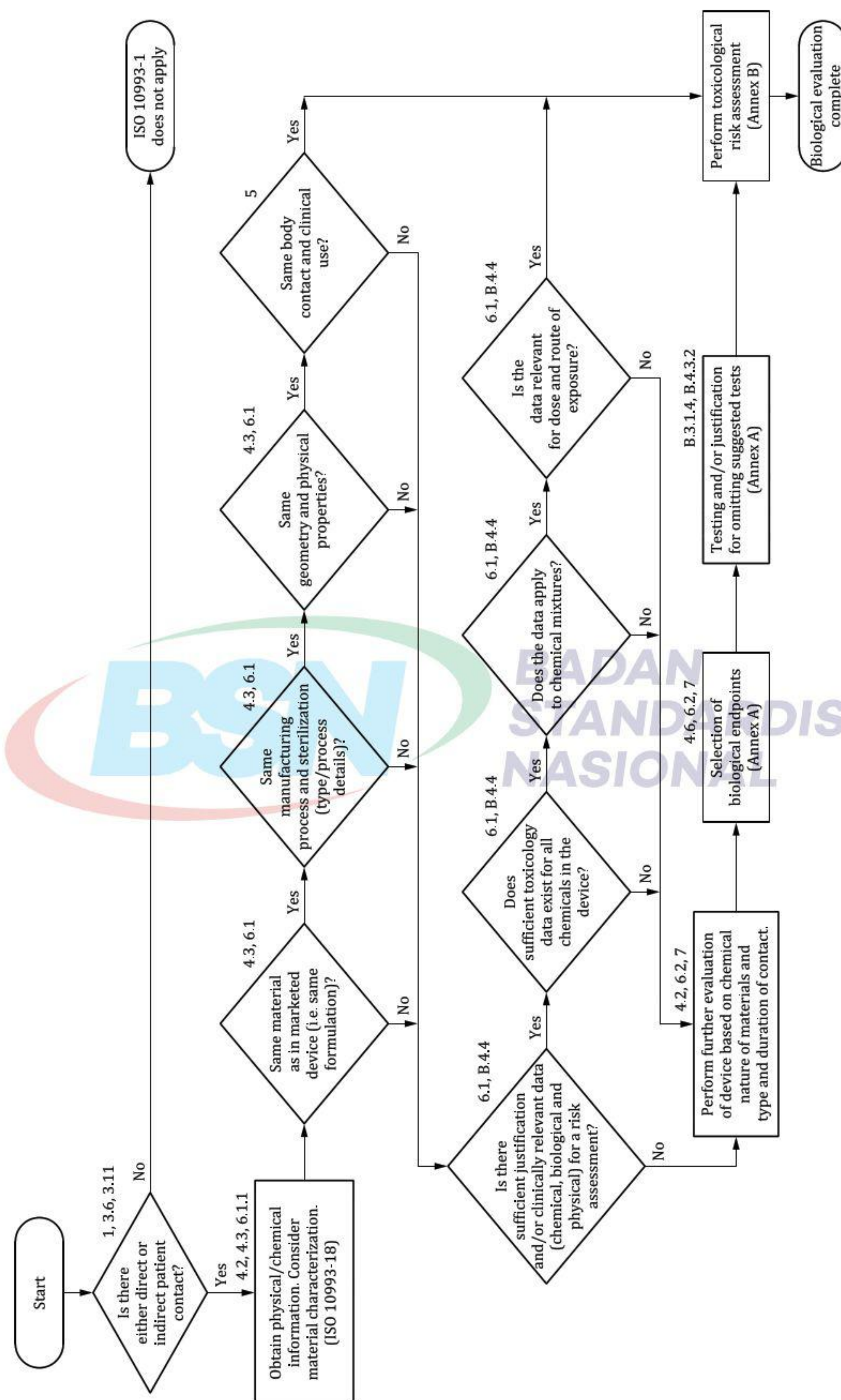



Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

4.9 The biological risk assessment of materials or final products shall be re-evaluated if any of the following occur:

a) any change in the source or in the specification of the materials used in the manufacture of the product;

b) any change in the formulation, processing, primary packaging or sterilization of the product;

c) any change in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life and/or transport;

d) any change in the intended use of the product;

e) any evidence that the product can produce adverse biological effects when used in humans.

4.10 The biological evaluation shall take into account preclinical tests, clinical investigations, post-market experience from similar medical devices or materials, and other relevant information (see Annex B).

4.11 This document shall not be used to mandate re-testing of historical products assessed previously using the appropriate edition of this document at the time of the assessment. Nevertheless, compliance to this new edition shall be shown, by providing a justification for omission of further testing. Where recommendations for endpoint assessment per Annex A are different from prior published versions of this document, a history of safe clinical use can be used to document why additional testing on a commercially-marketed medical device is not needed. However, if any of the changes described in Clause 4.9 occur, an evaluation of the biologic risks related to the change shall be performed using the current version of this standard.

5 Categorization of medical devices

5.1 General

Medical devices shall be categorized according to the nature and duration of body contact as specified in 5.2 and 5.3. The categorization of medical devices facilitates selection of appropriate data sets (see informative Annex A).

The evaluation of any medical device that does not fall into one of the categories specified shall follow the general principles contained in this document. Certain medical devices might fall into more than one body contact or duration category, in which case evaluation appropriate to each category shall be carried out.

EXAMPLE For medical devices that include both an implanted component, and a delivery system that is used only during a surgical procedure to place the medical device, the implant should be assessed separately from the delivery system.

EXAMPLE For gas pathway device components with only indirect contact, device specific standards should be used to determine the relevant type of biocompatibility evaluations [see ISO 18562 (all parts)].

5.2 Categorization by nature of body contact

5.2.1 Non-contacting medical devices

These include medical devices (or components) that have neither direct nor indirect contact with the body and where biocompatibility information would not be necessary. Diagnostic software, an *in vitro* diagnostic device and a blood-collection tube are examples of non-contact devices.

5.2.2 Surface-contacting medical devices

These include medical devices in contact with the following.

a) Skin

— Medical devices that contact intact skin surfaces only.

EXAMPLES Electrodes, external prostheses, fixation tapes, compression bandages and monitors of various types.

NOTE Some medical devices used in either sterile or non-sterile environments include components that can come into contact with a user's ungloved hands such as human interfaces for electronic equipment (e.g. computer keyboards, dials or buttons, touch screens, SD cards, USB sticks); housings for electronic monitors or programmers that can come into contact with any intact skin (e.g. electronic devices like cell phones, tablets); or components that can come into contact with a user's gloved hand (e.g. catheter handles). If these types of components can be shown to be made from materials in common use for other consumer products with a similar nature of contact, no further biological evaluation is needed.

b) Mucosal membranes

— Medical devices that contact intact mucosal membranes.

EXAMPLES Contact lenses, urinary catheters, intravaginal and intra-intestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, some dental prostheses and orthodontic devices.

c) Breached or compromised surfaces

— Medical devices that contact breached or otherwise compromised body surfaces.

EXAMPLES Dressings or healing devices and occlusive patches for ulcers, burns and granulation tissue.

5.2.3 Externally communicating medical devices

Externally communicating medical devices shall be categorized according to their contact with the following application sites.

a) Blood path, indirect

— Medical devices or components that do not necessarily directly contact the blood path directly but serve as conduits to deliver fluids into the vascular system.

EXAMPLES Solution administration sets, extension sets, transfer sets and blood administration sets.

b) Tissue/bone/dentin

— Medical devices that contact tissue, bone or pulp/dentin systems.

EXAMPLES Laparoscopes, arthroscopes, draining systems, dental filling materials and skin staples.

— Medical devices or components that do not necessarily directly contact tissue or bone but serve as conduits to delivery fluids to the tissue or bone.

EXAMPLES Tubing used for irrigation and medical device components that have fluid contact that can also contact the patient.

c) Circulating blood

— Medical devices that contact circulating blood.

EXAMPLES Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

5.2.4 Implant medical devices

Implant medical devices shall be categorized according to their contact with the following application sites.

a) Tissue/bone

— Medical devices principally contacting bone.

EXAMPLES Orthopaedic pins, plates, replacement joints, bone prostheses, bone cements and intra-osseous devices.

— Medical devices principally contacting tissue and tissue fluid.

EXAMPLES Pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, ligation clips and intrauterine devices that do not achieve their primary function by chemical activity.

b) Blood

— Medical devices principally contacting circulating blood in the cardiovascular system.

EXAMPLES Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug-delivery catheters and ventricular assist devices.

NOTE Most tissues contain circulating blood; however, this category is not intended to encompass devices implanted into tissue that contain transitory released blood (e.g. a hernia repair graft).

5.3 Categorization by duration of contact

5.3.1 Contact duration categories

Medical devices shall be categorized according to the anticipated duration of contact as follows.

a) Limited exposure (A) – medical devices whose cumulative sum of single, multiple or repeated duration of contact is up to 24 h.

b) Prolonged exposure (B) – medical devices whose cumulative sum of single, multiple or repeated contact time is likely to exceed 24 h but not exceed 30 d.

c) Long-term exposure (C) – medical devices whose cumulative sum of single, multiple or repeated contact time exceeds 30 d.

5.3.2 Transitory-contacting medical devices

Some medical devices with limited exposure (A) have very brief/transitory contact with the body (e.g. lancets, hypodermic needles, capillary tubes that are used for less than one minute). These generally would not require testing to address biocompatibility. However, for products made with materials such as coatings or lubricants that could be left in contact with body tissues after the medical device is removed, it is possible that a more detailed biocompatibility assessment will be necessary. Cumulative use should also be considered.

5.3.3 Medical devices with multiple contact duration categories

If a material or medical device can be placed in more than one duration category, the more rigorous testing and/or evaluation considerations shall apply. With expected or intended multiple exposures to a device, the decision into which category a medical device is placed shall take into account the potential

cumulative effect, bearing in mind the period of time over which these exposures occur. If a medical device is intended to change during its lifetime, such as those that are polymerized and/or degraded *in situ*, the evaluation shall consider all the different device states. For example, for an absorbable glue intended to polymerize *in situ*, the different device states would include starting components, intermediate reaction products, the fully polymerized material and degradation products.

6 Biological evaluation process

6.1 Physical and chemical information for biological risk analysis

Figure 1 indicates how the general steps in the physical and/or chemical characterization process link to the overall biological evaluation decision points.

Gathering physical and chemical information on the medical device or component is a crucial first step in the biological evaluation and its associated process of material characterization. These data should be sufficient to answer the first two rows of questions in the Figure 1 flow chart. The extent of physical and/or chemical characterization required depends on what is known about the material formulation, what nonclinical and clinical safety and toxicological data exist, and on the nature and duration of body contact with the medical device. At a minimum, the characterization shall address the constituent chemicals of the medical device and possible residual process aids or additives used in its manufacture. In addition, it is possible that some physical characterization information will be needed for implanted medical devices or medical devices in contact with blood. Material characterization, if performed, shall be conducted in accordance with ISO 10993-18. For nanomaterials see ISO/TR 10993-22.

If the combination of all materials, chemicals and processes has an established history of safe use in the intended application, and the physical properties have not changed, then it is possible that further characterization and additional data sets (e.g. chemical analysis of extracts or biological testing) will not be necessary. In this case the rationale shall be documented.

The identity and quantity of any novel materials and chemicals present should be established or measured.

For device extractables and leachables that have sufficient toxicological data relevant to the expected exposure (quantity, route and frequency), further testing need not be required. For medical devices that have known leachable chemical mixtures, potential interactions between the leachables should be considered.

Where the potential for degradation exists under the conditions of manufacture, sterilization, transport, storage, and use of the medical device, the presence and nature of degradation products shall be characterized in accordance with ISO 10993-9, ISO 10993-13, ISO 10993-14, and ISO 10993-15, as applicable.

For materials and/or medical devices that can release wear particles, the potential release of nanoparticles should be considered as described in ISO/TR 10993-22.

6.2 Gap analysis and selection of biological endpoints for assessment

Assess available information and compare to the data set(s) needed to assess the biological safety of the medical device (see Clause 4, Annexes A and C). Identify additional reasonably and practicably obtained data or testing needed to complete the data sets required to perform the risk assessment.

Characterize the data gap and determine its significance both to the assessment of the biological endpoint (Annex A) and to the overall biological risk assessment. Identify options for data sets that would address the data gap.

For example, pharmacopeial plastics' testing is typically conducted on raw materials, whereas ISO 10993 evaluates the medical device in its final stage. Therefore, data from such pharmacopeial testing is not sufficient for the final medical device without appropriate justification.

The results of the risk analysis of identified chemicals can lead to the conclusion that additional material characterization is necessary. Appropriate extraction testing, can be used to estimate the degree of clinical exposure to the chemical constituent (see ISO 10993-18). The acceptability of the level of estimated leachables shall be established by comparing the amount of each compound extracted from the medical device to its respective relevant toxicological threshold as developed in accordance with ISO 10993-17.

NOTE For example, when the margin of safety is not considered adequate if the entire amount of a particular chemical is leached out during use, appropriate extraction testing can be used.

Protection of humans is the primary goal of this document; a secondary goal is to ensure animal welfare and to minimize the number and exposure of the test animals. ISO 10993-2 applies to any *in vivo* testing being considered. Additional *in vivo* testing shall not be carried out where

1) results are available from relevant studies that have been carried out previously, or

2) the existing non-clinical and clinical data, including history of safe use, meet the requirements of biological evaluation and therefore further animal testing would be unethical. In assessing the relevance of data on prior use of a material to the biological evaluation, the level of confidence in the historical data should be taken into account. ISO 10993-18:2005, Annex C, gives some informative principles for judging chemical equivalence.

6.3 Biological testing

6.3.1 General

In addition to the general principles given in Clause 4, the following shall apply when biological testing of medical devices is considered necessary as part of the overall risk management process.

a) Testing shall be performed on the final medical device, or representative samples from the final device or materials processed in the same manner as the final medical device (including sterilization, if needed).

b) The choice of test procedures shall take into account:

   1) the nature, degree, duration, frequency and conditions of exposure to or contact of humans with the medical device in the normal intended use;

   2) the chemical and physical nature of the final medical device;

   3) the toxicological activity of the chemicals in the formulation of the final medical device;

   4) that certain biological tests (i.e. those designed to assess systemic effects) are not justifiable where the presence of leachable chemicals has been excluded (in accordance with ISO 10993-18), or where chemicals have a known and acceptable toxicity profile, allowing the safe use by evaluation in accordance with ISO 10993-17 and risk assessment in accordance with ISO 14971;

   5) the ratio of device surface area to recipient body size and mass (e.g. device miniaturization for implantation testing in animal models);

   6) the existing information based on the literature, previous experience and non-clinical tests;

   7) the sensitivity and specificity of the test being considered in relation to the impact of the resulting data set on the biological evaluation;

   8) that ISO 10993-2:2006, 4.4, requires that any pain, suffering, distress or lasting harm to the animals used shall be minimized.

c) If extracts of the medical devices are prepared, the solvents and conditions of extraction used should be appropriate to the nature and use of the final product, as well as to the predictability

(such as test purpose, rationale, sensitivity, specificity, etc.) of the test method, and shall be prepared in accordance with ISO 10993-12. Whenever possible, the extraction conditions selected should represent at a minimum, an exaggeration of use conditions.

d) Positive and negative controls should be used where appropriate.

The test methods used in the biological evaluation tests shall be sensitive, precise and accurate. When biological testing is conducted, it shall be carried out in accordance with good laboratory practices.

NOTE ISO/IEC 17025 or equivalent.

The test methods should be reproducible (intralaboratory) as well as repeatable (interlaboratory) and robust.

6.3.2 Testing for evaluation

Testing for the evaluations specified in 6.3.2.1 to 6.3.2.15 shall be considered and carried out where necessary to complete the data sets needed for the biological evaluation of the particular medical device. Where the existing data are adequate, additional testing is not required (see Annexes A and C).

Due to the diversity of medical devices, it is recognized that testing will not be necessary or practicable for all endpoints identified in a category (see ISO 14971) for a given medical device. It is indispensable for evaluations that each medical device be considered on its own merits. Nanomaterials can pose specific challenges (e.g. assay interference) when applying test systems commonly used for medical device evaluation and when interpreting test results (see ISO/TR 10993-22).

Additional endpoints not indicated in the table can be necessary (e.g. reproductive toxicity, developmental toxicity, degradation and toxicokinetics).

6.3.2.1 Cytotoxicity

Cytotoxicity tests employing cell culture techniques can be used to determine the cell death (e.g. cell lysis), the inhibition of cell growth, colony formation, and other effects on cells caused by medical devices, materials and/or their extracts. If testing is performed, it shall be conducted in accordance with ISO 10993-5.

6.3.2.2 Sensitization

Sensitization (e.g. delayed-type hypersensitivity) tests can be used to estimate the potential for contact sensitization by medical devices, materials and/or their extracts, using an appropriate model. If testing is performed, it shall be conducted in accordance with ISO 10993-10.

These tests are important because repeat exposure or contact to even very small amounts of potential leachables can result in sensitization, which can lead to allergic reactions.

6.3.2.3 Irritation (including intracutaneous reactivity)

Irritation tests can be used to estimate the irritation potential of medical devices, materials and/or their extracts, using an appropriate site for application such as skin, eye and mucous membrane in a suitable model. The test(s) performed shall be appropriate for the route (skin, eye, mucosa) and duration of exposure or contact, and shall be conducted in accordance with ISO 10993-10.

The intracutaneous reactivity test can be used to assess the localized reaction of tissue to medical device extracts. This test is applicable where the determination of irritation by dermal or mucosal tests is inappropriate (e.g. where medical devices are implanted or have blood contact). This test might also be useful where extractables are hydrophobic (see ISO 10993-10).

6.3.2.4 Haemocompatibility

Haemocompatibility tests can be used to evaluate, using an appropriate model or system, the effects of blood-contacting medical devices or materials on blood or blood components.

One haemocompatibility test, haemolysis, determines the degree of red cell lysis and the release of haemoglobin caused by medical devices, materials, and/or their extracts *in vitro*.

Other specific haemocompatibility tests can also be designed to simulate the geometry, contact conditions and flow dynamics of the medical device or material during clinical applications and determine blood/material/device interactions.

Any testing performed shall be conducted in accordance with ISO 10993-4.

6.3.2.5 Material-mediated pyrogenicity

Pyrogenicity tests as part of a biological evaluation are intended to detect material-mediated pyrogenic reactions of extracts of medical devices or materials. No single test can differentiate pyrogenic reactions that are material-mediated from those due to endotoxin contamination (see ISO 10993-11:2017, Annex G). Material-mediated pyrogenicity is rare. It has been observed in medical devices containing biologically-derived materials.

6.3.2.6 Acute systemic toxicity

Acute systemic toxicity tests can be used where contact allows potential absorption of toxic leachables and degradation products, to estimate the potential harmful effects of either single or multiple exposures, during a period of less than 24 h, to medical devices, materials and/or their extracts in an animal model. These tests shall be appropriate for the route of exposure, and any testing performed shall be conducted in accordance with ISO 10993-11.

If feasible, acute systemic toxicity tests can be combined with subacute and subchronic toxicity and implantation test protocols.

Where an evaluation of systemic toxicity is specified in Table A.1, biological testing or the risk assessment shall include assessment of the potential for biological responses in tissues throughout the body (e.g. per ISO 10993-11:2017, Annex E), including the organ systems relevant to the clinical use of the medical device.

6.3.2.7 Subacute and subchronic toxicity

Subacute and subchronic toxicity tests can be carried out to determine the effects of either single or multiple exposures or contact to medical devices, materials and/or their extracts for a period not less than 24 h to a period not greater than 10 % of the total life-span of the test animal (e.g. up to 13 weeks in rats).

These tests shall be waived if available data for the chronic toxicity of the relevant materials are sufficient to allow the subacute and subchronic toxicity to be evaluated. The reason for waiving of the tests shall be included in the overall biological evaluation report. These tests shall be appropriate for the route and duration of contact.

Subacute and subchronic toxicity tests, if performed, shall be conducted in accordance with ISO 10993-11.

If feasible, subacute and subchronic systemic toxicity test protocols can be expanded to include implantation test protocols to evaluate subacute and subchronic systemic and local effects.

6.3.2.8 Chronic toxicity

Chronic toxicity tests can be used to determine the effects of either single or multiple exposures to medical devices, materials and/or their extracts during a major period of the life-span of the test animal

(e.g. usually 6 months in rats). These tests shall be appropriate for the route and duration of exposure or contact, and if performed, shall be conducted in accordance with ISO 10993-11.

If feasible, chronic systemic toxicity test protocol can be expanded to include an implantation test protocol to evaluate both chronic systemic and local effects.

6.3.2.9 Implantation effects

Implantation tests can be used to assess the local pathological effects on living tissue, at both the gross level and microscopic level, of a sample of a material or final product that is surgically implanted or placed in an implant site or tissue appropriate to the intended application (e.g. special dental usage tests). These tests shall be appropriate for the route and duration of contact, and if performed, shall be conducted in accordance with ISO 10993-6.

If feasible, implantation test protocols can be expanded to evaluate both local and systemic effects to meet acute, subacute, subchronic, and chronic toxicity testing requirements (see ISO 10993-6). If applicable and feasible, evaluation of haemocompatibility aspects can be included (see ISO 10993-4).

When appropriately designed simulated use animal studies are planned, it is anticipated that these studies will be used to address a range of endpoints including both physical and biological risk (i.e. toxicological hazard and/or toxicological risk). For instance, chronic/subchronic/subacute and acute systemic toxicity endpoints can be built into a single study. One can consider an experimental design where a clinically relevant quantity of material is implanted in the relevant organ or tissue to assess local effects, and an exaggeration of the anticipated clinical exposure/dose is implanted possibly at a remote location so the systemic exposure provides a suitable measure of exaggeration.

6.3.2.10 Genotoxicity

Genotoxicity tests can be used to assess the potential for gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by medical devices, materials and/or their extracts. A battery of *in vitro* tests is initially used. If testing is performed, it shall be conducted in accordance with ISO 10993-3.

NOTE Additional information is given in ISO/TR 10993-33.

If any of the *in vitro* tests are positive, follow-up can include a chemical identification of impurities, extractable or leachable chemicals or additional genotoxicity testing. Acceptance of the genotoxicity risk shall be based on the results of a risk assessment, including, for example patient exposure, weight of evidence (WOE) and mode of action (MOA) information, if available.

6.3.2.11 Carcinogenicity

ISO 10993-3 discusses the strategy for evaluating carcinogenicity of medical devices, materials and/or their extracts over a period of the major portion of life-span of the test animal. Carcinogenicity may be addressed with a risk assessment including chemical identification of impurities, extractable or leachable chemicals, patient exposure to these chemicals, weight of evidence (WOE) and mode of action (MOA) information, if available. Carcinogenicity information should be appropriate for the route and duration of exposure or contact, and can be available from the toxicity literature. In the absence of any significant cancer risk, it is rare for carcinogenicity tests to be considered appropriate for medical devices. However, if it is determined that carcinogenicity testing of the final medical device is needed, it is possible that lifetime studies or transgenic models will be appropriate. It is also possible that these tests can be designed to examine both chronic toxicity and tumorigenicity in a single experimental study, as described in OECD Guideline 453.

6.3.2.12 Reproductive and developmental toxicity

Reproductive and developmental toxicity tests referenced in ISO 10993-3 can be used to evaluate the potential effects of medical devices, materials and/or their extracts on reproductive function, embryonic development (teratogenicity), and prenatal and early postnatal development. These

endpoints may be addressed with a risk assessment including chemical identification of impurities, extractable or leachable chemicals, patient exposure to these chemicals, weight of evidence (WOE) and mode of action (MOA) information, if available. Reproductive toxicity evaluations shall only be conducted when the medical device has potential impact on the reproductive potential of the subject. In addition, developmental toxicity evaluations should be considered for medical devices or their materials used during pregnancy.

Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of medical device materials in the reproductive organs.

6.3.2.13 Degradation

Degradation information shall be provided for any medical devices, medical device components or materials remaining within the tissue, that have the potential for degradation within the human body.

Degradation tests shall be considered if

a) the medical device is designed to be absorbable, or

b) an informed consideration of the finished medical device composition indicates that toxic degradation products might be released during body contact.

Parameters that affect the rate and extent of degradation shall be described and documented.

The mechanisms of degradation should be described. These mechanisms should be simulated *in vitro* to determine the rates of degradation and release of potentially toxic chemicals to estimate the exposure. It is also possible that *in vivo* tests will be required to assess degradation of a material.

In vivo degradation tests might not be necessary if an *in vitro*/*in vivo* comparison for the absorbable medical device has been previously demonstrated and *in vitro* degradation studies show that only the probable products of degradation are present in the predicted quantities, and produced at a rate similar to those that have a history of safe clinical use. When particulate degradation products are generated, tests might not be necessary if they are present in a physical state, i.e. size distribution and shape, similar to those with a history of safe clinical use or sufficient degradation data already exist relevant to the substances and degradation products generated in the intended use already exists.

A general framework for degradation tests is given in ISO 10993-9.

Specific *in vitro* degradation tests for polymers, ceramics and metals are described in ISO 10993-13, ISO 10993-14 and ISO 10993-15 respectively.

When particulate degradation products are present in the form of nanomaterials, tests should be designed considering ISO/TR 10993-22.

6.3.2.14 Toxicokinetic studies

The purpose of conducting toxicokinetic studies is to evaluate the absorption, distribution, metabolism and excretion (ADME) of a chemical.

The need for *in vivo* toxicokinetic studies, to determine the processes of absorption, distribution, metabolism and elimination of leachables and degradation products of medical devices, materials and/or their extracts (see 6.3.2.13 and ISO 10993-16), shall be considered in the light of results from the *in vitro* degradation studies.

When deciding whether or not to conduct toxicokinetic studies as part of the biological evaluation of a medical device, the final product and its chemical constituents, including potential and designed degradation products and leachables in combination with the intended use of the medical device, shall all be taken into account (see 6.3.2.13).

Where appropriate, theoretical degradation processes shall be investigated prior to toxicokinetic studies by means of *in vitro* experiments (e.g. tissue, homogenates or cells), not only for animal welfare reasons as given in ISO 10993-2, but also to determine probable rather than possible degradation products.

Toxicokinetic studies shall be considered if

a) the medical device is designed to be absorbable, or

b) the medical device is a long-term contact implant, and degradation or significant corrosion is known or likely, and/or migration of leachables from the medical device occurs, or

c) the medical device is likely or known to release substantial quantities of potentially toxic or reactive degradation products and leachables into the body during clinical use, or

d) substantial quantities of nano-objects are likely or known to be released from a medical device into the body during clinical use, or

e) drug and device combination products.

Toxicokinetic studies are not required if the achieved or expected rates of release of degradation products and leachables from a particular medical device or material have been judged to provide safe levels of clinical exposure with historical experience, or if sufficient toxicological data or toxicokinetic data relevant to the degradation products and leachables already exist.

The release of leachables and degradation products from metals, alloys and ceramics is usually too low to justify toxicokinetic studies, unless the material is designed to degrade.

Toxicokinetic studies for degradation products and extractables/leachables, if performed, shall be conducted in accordance with ISO 10993-16.

Specific considerations for toxicokinetics studies with nanomaterials are given in ISO/TR 10993-22

6.3.2.15 Immunotoxicology

While not specifically addressed in Annex A, ISO/TS 10993-20 provides an overview of immunotoxicology with particular reference to the potential immunotoxicity of medical devices. Immunotoxicity testing shall be considered based on the chemical nature of the materials of manufacture and data from sources that are suggestive of immunotoxicological effects or if the immunogenic potential of any of the chemicals is unknown. If immunotoxicity testing is performed, it shall be conducted in accordance with ISO/TS 10993-20.

Specific considerations for immunotoxicity testing of nanomaterials are provided in ISO/TR 10993-22.

7 Interpretation of biological evaluation data and overall biological risk assessment

Expert assessors who have the necessary knowledge and experience shall determine and document:

a) the strategy and planned content for the biological evaluation of the medical device;

b) the criteria for determining the acceptability of the material for the intended purpose, in line with the risk management plan;

c) the adequacy of the material characterization;

d) the rationale for selection and/or waiving of tests;

e) the interpretation of existing data and results of testing;

f) the need for any additional data to complete the biological evaluation;

g) overall biological safety conclusions for the medical device.

Informative Annex A gives the general endpoints that should be considered for each device contact type and duration category in a biological risk assessment.

Annex A
(informative)

Endpoints to be addressed in a biological risk assessment

A.1 General

The following is a framework for the development of a biocompatibility evaluation and is not a checklist for testing. Where Table A.1 indicates that an endpoint is relevant for assessment, the existing data sets relevant to that endpoint should be evaluated to determine if any additional data sets are needed. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

In Table A.1; X means prerequisite information needed for a risk assessment; E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set assessment)

Any variation should be justified in the biological risk assessment. If there are device specific standards that include specific recommendations regarding biocompatibility, these should be considered.

Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/bone/dentin[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E[j]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

Table A.1 *(continued)*

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Implant medical device	Tissue/bone [i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

[a] Refer to ISO 10993-11:2017, Annex F.

[b] Information obtained from comprehensive implantation assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity and/or chronic toxicity may be appropriate if sufficient animals and timepoints are included and assessed. It is not always necessary to perform separate studies for acute, subacute, subchronic, and chronic toxicity.

[c] Relevant implantation sites should be considered. For instance medical devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes.

[d] If the medical device can contain substances known to be carcinogenic, mutagenic and/or toxic to reproduction, this should be considered in the risk assessment.

[e] Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs.

[f] Degradation information should be provided for any medical devices, medical device components or materials remaining within the patient, that have the potential for degradation.

[g] X means prerequisite information needed for a risk assessment.

[h] E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why assessment of the endpoint does not require an additional data set). If a medical device is manufactured from novel materials, not previously used in medical device applications, and no toxicology data exists in the literature, additional endpoints beyond those marked "E" in this table should be considered. For particular medical devices, there is a possibility that it will be appropriate to include additional or fewer endpoints than indicated.

[i] Tissue includes tissue fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these medical devices.

[j] For all medical devices used in extracorporeal circuits.

A.2 Rationale for endpoints in Table A.1

The following endpoints were not included in the fourth edition (2009) of this document. The rationale for inclusion of each endpoint with this revision is addressed below.

— **Physical and/or chemical information (all medical device categories, with all types of contact, and all durations of contact).**

  This information is used for all medical device types to determine whether further biological testing is needed.

— **Irritation or intracutaneous reactivity (externally communicating medical devices, with indirect blood path contact, and a long term duration).**

  Components with long term indirect contact with blood (e.g. infusion systems) can introduce irritants into the blood stream that should be addressed as part of the biological risk assessment.

— **Material mediated pyrogenicity and acute systemic toxicity (medical devices with breached or compromised surface contact and all durations of contact).**

  Extractables/leachables can be introduced to the systemic circulation through breached or compromised surfaces, and therefore both material mediated pyrogenicity and acute systemic toxicity should be considered.

— **Material mediated pyrogenicity (externally communicating medical devices and implant medical devices with all types of contact, and all durations of contact).**

  Extractables/leachables can be introduced to the systemic circulation, lymphatic system, and/or cerebrospinal fluid, and therefore material mediated pyrogenicity should be considered.

— **Acute systemic toxicity (surface medical devices with mucosal membrane contact, and prolonged or long term contact; and externally communicating medical devices with tissue/ bone/dentin contact for a limited duration; and implant medical devices with tissue/bone contact for a limited duration).**

  Extractables/leachables can be introduced via mucosal membranes and to the systemic circulation, lymphatic system, and/or cerebrospinal fluid, and therefore acute systemic toxicity should be considered.

— **Subacute toxicity (all medical device types with prolonged and long term contact).**

  For medical devices/components with more than 24 hours use, extractables/leachables can be introduced to the systemic circulation, lymphatic system, and/or cerebrospinal fluid, and therefore subacute toxicity should be considered.

— **Subchronic and chronic toxicity (all medical device types with long term contact).**

  For medical devices/components with at least 30 day use, extractables/leachables can be introduced to the systemic circulation, lymphatic system, and/or cerebrospinal fluid, and therefore subchronic and/or chronic toxicity should be considered.

— **Implantation effects (surface medical devices with mucosal membrane contact, and prolonged or long term contact; and surface medical devices with breached or compromised surface contact, and prolonged or long term contact).**

  For medical devices/components with this type of contact, local and systemic effects from implantation should be considered. For medical devices/components where repeat use could change the category from limited to prolonged or long-term duration, information on potential for accumulation of chemicals in the tissue can be used to inform whether implantation testing should be considered.

— **Implantation effects (externally communicating medical devices, with indirect blood path contact, and a long term duration).**

Components with long term indirect contact with blood (e.g. infusion systems) can introduce extractables/leachables into the blood stream that could impact the inflammatory response to direct contacting components of the medical device (if applicable). If literature is available to address systemic toxicity of all extractables/leachables, and there is no direct contacting component, it is possible that implantation assessments will not be needed for this category.

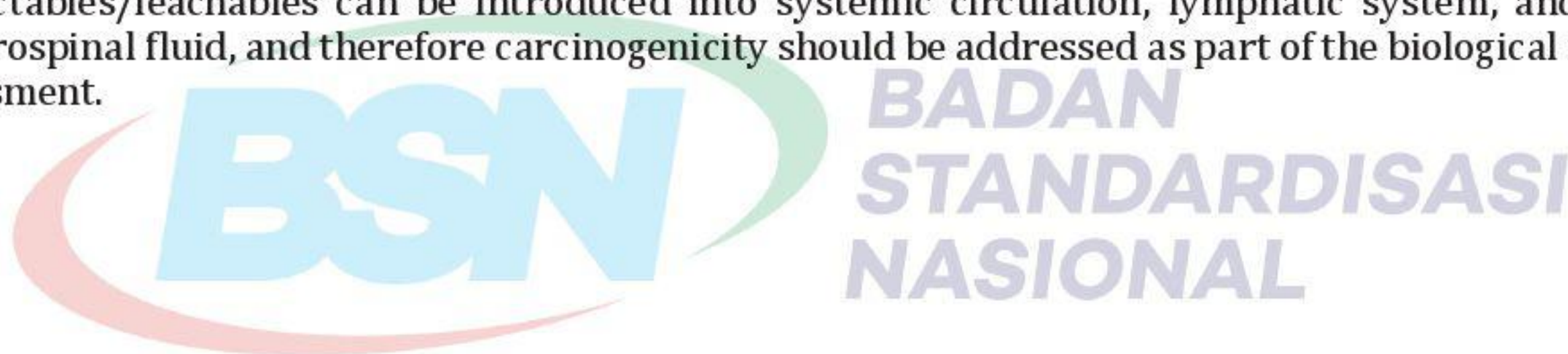
— **Genotoxicity (externally communicating medical devices, with circulating blood contact for a limited duration).**

For medical devices/components used in extracorporeal circuits, extractables/leachables can be introduced into the blood stream and remain after the medical device is removed, and therefore genotoxicity should be considered.

— **Genotoxicity (implant medical devices, with blood contact for a limited duration).**

Extractables/leachables can be introduced into the blood stream and remain after the medical device is removed, and therefore genotoxicity should be considered.

— **Carcinogenicity (surface medical devices with breached or compromised surface contact for a long term duration; and all externally communicating medical devices and implant medical devices with a long term duration).**

Extractables/leachables can be introduced into systemic circulation, lymphatic system, and/or cerebrospinal fluid, and therefore carcinogenicity should be addressed as part of the biological risk assessment.

Annex B
(informative)

Guidance on the conduct of biological evaluation within a risk management process

B.1 Background information

B.1.1 General

This annex provides guidance on conduct of biological evaluation of medical devices according to the requirements of this document. Although this document provides a general framework for biological evaluation of medical devices, more detailed guidance can be helpful in the practical application of this document. As a result, this Annex was developed to provide such guidance to users. This guidance can be used to better understand the requirements of this document and to illustrate some of the various methods and approaches available for meeting the requirements.

Biological evaluation is a design verification activity which is set in the context of broader risk management processes. Therefore this annex includes guidance on the application of this document in the context of risk management processes conducted according to the requirements of ISO 14971. This annex describes concepts and methods that can be considered in establishing and maintaining a risk management process for biological evaluation as part of the overall evaluation and development of a medical device.

As scientific knowledge advances our understanding of the basic mechanisms of tissue responses, the way biological evaluation is carried out can also change, moving towards an evaluation based upon review of relevant established scientific data and upon physical and chemical characterization and *in vitro* testing, with *in vivo* testing only being carried out where these are required to fill gaps in our understanding. This document specifies a framework in which to plan a biological evaluation which minimizes the number and exposure of test animals by giving preference to identifying chemical constituent testing and *in vitro* models in situations where these methods yield equally relevant information to that obtained from *in vivo* models. The selection of which approach(es) are applicable to a particular medical device will depend on the nature of the medical device, the extent of available relevant scientific data and upon risk assessment.

When judging the applicability of the guidance in this annex, applicable regulatory requirements and regulatory guidance should be considered.

An organization can voluntarily incorporate guidance from this annex, wholly or in part, into its risk management process.

Guidance contained in this annex can be useful as background information for those representing risk management process assessors, conformity assessment bodies and regulatory enforcement bodies.

B.1.2 Relationship with other standards, guidance documents and regulatory requirements

The relationship between this document, this annex and the standards for biological evaluation of medical devices and general risk management is summarized as follows:

— this annex provides guidance on the application of this document;

— biological evaluation is a component of risk management and this Annex includes guidance on the application of ISO 14971 to the conduct of biological evaluation.

This annex does not add to, or otherwise change, the requirements of this document. This annex does not include requirements to be used as the basis of regulatory inspection or certification assessment activities.

B.2 Biological evaluation as a risk management practice

B.2.1 General

B.2 and B.3 describe a continuous process by which a manufacturer can identify the biological hazards associated with medical devices, estimate and evaluate the risks, control these risks, and monitor the effectiveness of the control. Appropriate protection of the patient should be achieved by implementing a biological evaluation plan which includes, as an essential element the weighing of the risks and benefits of medical devices. Benefit to the patient from the use of medical devices entails the acceptance of potential risks. These risks will vary depending on the nature and intended use of the specific medical device. The level of risk which is acceptable for a specific medical device will depend upon the expected benefit provided by its use.

Consideration of biological risk is only one aspect of the risk assessment of a medical device, which should consider all aspects of risk. In some cases it can be specifically necessary to consider the relative benefits of materials of different biological safety profiles in the context of some other characteristic. For example it can be possible that the most biologically safe material available can have unacceptable mechanical strength, in which case it would be necessary to consider if an alternate stronger material is of acceptable biological safety. It is fundamental to the conduct of biological evaluation that it be undertaken as part of the overall risk management process required in the design and development of the medical device.

Material selection and risk analysis are integral components of the design process for medical devices. The selection of materials plays a crucial role in evaluating the biological safety and, when approached in a systematic way, allows the collection of relevant data. In line with ISO 13485 and ISO 14971, criteria to define the acceptable biological risk should be established at the start of the design process. Because starting material, formulation and processing variations including packaging, transportation and aging could impact final product biocompatibility; these considerations should also be incorporated into the risk assessment. The biological evaluation should be designed and performed to demonstrate the achievement of specified criteria for safety based on outputs of the risk analysis and/or history of use of the same material. This evaluation is a component of the risk management plan encompassing identification of all hazards and the estimation of associated risks. Adequate risk assessment requires characterization of toxicological hazards and exposures, as well as other potential biological responses to medical devices.

A major component in hazard identification is material characterization (see ISO 10993-18 and ISO/TR 10993-19). The following steps can be identified:

— define and characterize each material, including suitable alternative materials;

— identify hazards in materials, additives, processing aids, etc.;

— identify the potential effect of downstream processing (e.g. chemical interactions between material components, or final product sterilization) on chemicals present in final product;

— identify the chemicals that could be released during product use (e.g. intermediate or final degradation products from a degradable implant);

— estimate exposure (total or clinically available amounts);

— review toxicology and other biological safety data (published/available).

Information on biological safety to be reviewed can include:

— toxicology data on relevant component materials/compounds;

— information on prior use of relevant component materials/compounds;

— data from biological tests.

The risks posed by the identified hazards should then be evaluated. At this stage it should be possible to determine whether there is an undue toxicological risk from the material.

If it can be concluded from existing data that risks are acceptable then no additional testing is needed to support biological safety. Testing should not be conducted if risks are found to be unacceptable. When existing data are insufficient, additional information should be obtained. The purpose of testing is to obtain additional data which can assist in reaching a conclusion. A rationale for testing should therefore be based on an analysis of the relevant risks which are indicated from the existing data.

The results of any tests should be assessed. Test reports should include descriptive evidence, an assessment of the findings and qualitative assessment of their acceptability.

The assessor should determine if the available information is sufficient to meet the purpose of the evaluation of biological safety and if so document how the conclusion on safety was reached including the rationale for any decisions and the impact of test results and other information on the assessment.

The evaluation should be documented in a report that indicates the identity and significance of all relevant evidence and highlights the scientific basis of the overall conclusions in an accurate, clear and transparent manner. It is very important that the factors leading to the conclusion are fully discussed with succinct and accurate rationales for each judgment and identification and discussion of any uncertainties underlying each decision.

The components of risk management are summarized in Figure B.1 (taken from ISO 14971). The different elements of a biological evaluation process can be considered in terms of the elements of the overall risk management process.

In summary, biological evaluation should be seen as an element of risk management practice and therefore the conduct of a biological evaluation of a medical device should aim to meet both the requirements of this document and ISO 14971.

B.2.2 The biological evaluation plan

ISO 14971:2007, 3.4, requires that risk management activities be planned in advance. Since biological evaluation is a risk management activity, a Biological Evaluation Plan is required, and this forms part of the Risk Management Plan. It is emphasized that simply planning to conduct testing against all of the aspects of biocompatibility identified in Annex A does not meet the requirements of ISO 14971 or this document. An example of how this guidance can be applied to a medical device can be seen in ISO 18562-1.

The biological evaluation plan should be drawn up by a knowledgeable and experienced team and include as a minimum:

— arrangements for gathering of applicable information from the published literature (including information sources and search strategies), in house and supplier data and other sources in order to conduct risk analysis;

— arrangements for conducting the evaluation, including the requirement for any specific technical competencies relevant to the specific medical device application;

— arrangements for review and approval of the plan as part of the overall design control process;

— arrangements for review of the final conclusions of the evaluation and the approval of any additional testing required;

— arrangements for the final review and approval of the outcomes of the biological risk assessment, including the risk control measures applied and the documentation of any residual risks and the disclosure of residual risks through means such as product labelling.

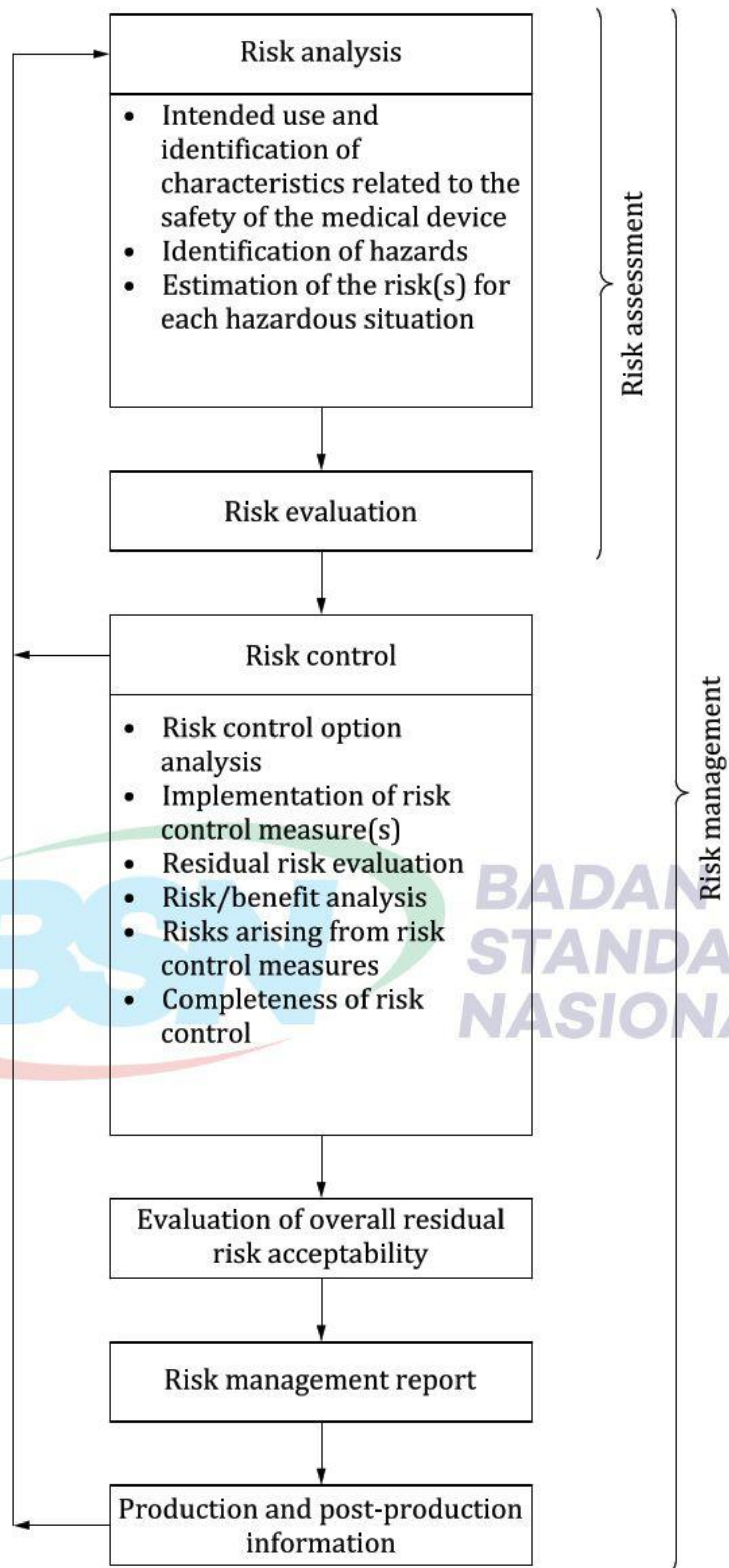



Figure B.1 — A schematic representation of the risk management process (taken from ISO 14971)

B.3 Guidance on risk management

B.3.1 Risk assessment

B.3.1.1 Introduction

Risk assessment is the combination of the processes of risk analysis in which risks are identified and estimated and risk evaluation in which risks are evaluated to identify those which require mitigation (risk control).

B.3.1.2 Risk analysis

Risk analysis is the process of identifying the specific hazards and assessing their significance. In a biological evaluation, one important consideration is the potential toxicity of materials components and their route of exposure. Another important consideration is how physical properties could affect the biological response. Risk analysis should be methodically conducted by means of estimation of risks from each material/component for each route of exposure and toxicological effect.

Risk analysis therefore begins with identification and characterization of the indirect and direct tissue-contacting materials and components of the medical device. This should be done based on the final form of the medical device in its manufactured state, taking into account the presence of any manufacturing additives, processing aids or other potential contaminants such as sterilant residues. Effects of processing on materials composition and chemistry (including both bulk and surface effects) should also be considered. In particular, where reactive or hazardous ingredients have been used in, or can be formed by, the production, processing, storage or degradation of a material, the possibility of the presence of toxic residues should be considered. The potential for interactions with or introduction of contaminants from packaging materials should also be considered.

Physical and chemical material properties are relevant to biological safety and will need to be identified at this stage. These can include one or more of the following:

— wear, load, fatigue, e.g. especially in load bearing medical devices such as total joint prostheses and the associated production of particulates (which could include nanomaterials) or materials degradation;

— friction and associated irritation, e.g. in applications such as catheters;

— interactions between material combinations (chemical interactions), e.g. different flexibility, galvanic corrosion, abrasion;

— heat (e.g. thermal degradation or other thermally induced material changes);

— manufacturing processes, e.g. internal stresses produced can promote environmental stress cracking (ESC), morphological changes, or degradation;

— environmental interactions, e.g. endoscope (stomach acids), dressings (external environment), UV-light, detergents, decontamination and sterilization processes;

— electricity, e.g. short circuits, degradation, heating, muscle stimulation;

— potential interactions between components;

— effect of physical form, e.g. particulates, which could include nanomaterials;

— processing;

— transportation and aging.

Materials information can be obtained through review of literature, vendor data, in house data or comparison with existing products on the market where the manufacturing processes and formulations are known and the same as in the medical device under evaluation.

NOTE 1 Informative Annex C provides guidance on conduct of literature review.

Chemical characterization should then be followed by consideration of the toxicology of the known material components. This specific nature of the toxic effect(s) and the dose-response relationship should be considered.

The range of toxicological effects is wide. Clause 5 and Informative Annex A provide guidance to relevant toxic effects for different exposure routes and durations.

In addition to characterization of extractables and leachables, physical properties of the medical device that could adversely impact the biological response to the medical device should be considered, such as geometry, stiffness, etc.

NOTE 2 For the characterization and testing of particulates, nanomaterials require specific attention, because materials with sub-micron components (e.g. nanomaterials) have been shown, in some cases, to behave differently than the same materials at larger scales, and extrapolation of data from larger sized materials is not appropriate.

B.3.1.3 Risk estimation

From a chemical toxicity perspective, risk estimation in addition to consideration of the toxicology of identified materials components also includes consideration of the anticipated exposure, e.g. the bioavailability of leachable or soluble components (see ISO 10993-17). From a material property perspective, risk estimation also includes exposure that might be anticipated due to the use of the medical device.

Risk is typically estimated by assigning values to the probability of occurrence of harm and the severity of that harm. In general toxicological terms, likelihood can be estimated from knowledge of the actual availability of toxic components and the known dose response in relevant tissue(s). The severity can be assessed in terms of the nature of the toxic response. From a material property perspective, likelihood can be estimated from physical testing such as for wear debris, and severity can be assessed in terms of the nature of the biological response from literature or animal studies.

If insufficient information is available from published literature, in-house data and documented clinical history of the subject medical devices or materials, risk estimation can require conduct of chemical or physical characterization or biological testing to estimate or quantify the hazards which cannot be satisfactorily determined from prior knowledge. Such investigations should be conducted in accordance with applicable parts of ISO 10993.

Test selections for risk estimation purposes can only be determined after the completion of the review of existing knowledge, as the tests should be specifically selected to address the deficiencies in knowledge identified in the review (see Annex C).

The amount of data required for risk analysis and the depth of the analysis will vary with the intended use and are dependent upon the nature and duration of tissue contact. Data requirements are usually less stringent for materials with indirect patient contact, medical devices contacting only intact skin, and any component of a medical device that does not come into direct contact with body tissues, infusible liquids, mucous membranes or compromised skin.

B.3.1.4 Risk evaluation

Risk evaluation builds upon the risk analysis, taking the next step of evaluating the risks defined in the risk analysis for their significance and identifying requirements and opportunities for mitigation (risk control). It should be realized that for a full evaluation the whole medical device should be taken into consideration including all its components.

Biocompatibility can only be demonstrated for a particular material in relation to a defined set of circumstances, which include the purpose for which it is used and the tissues with which it comes into contact. For example, the consideration of toxicology of extractable/leachable chemicals should be undertaken in context of the routes and duration of exposure and implications for actual availability of potential toxicants. Of particular importance is consideration of any history of clinical use or human exposure data from relevant similar applications. For example, clinical studies showing a final product is a non-irritant might be useful in justifying omission of animal irritation studies. However, clinical studies of a general implant material might not be sufficient to justify omission of a final product implant study, as the combination of materials might result in an adverse biological effect.

It is critical for the integrity of a biological risk evaluation that it should be conducted by assessors with the necessary knowledge and expertise to determine the appropriate strategy for the evaluation and ability to make a rigorous assessment of the available data and to make sound judgments on the requirements for any additional testing. (See Clause 7).

B.3.2 Risk control

Risk control is the process of identifying and implementing measures to reduce risks. In the context of biological safety this can involve activities such as consideration of options for design changes. Examples of possible strategies include:

— design changes to avoid more hazardous exposure routes or reduce exposure time;

— design changes to optimize geometric surface properties to minimize areas where low blood flow could result in thrombus formation;

— design changes to avoid medical device failures (e.g. particulation, or coating delamination) that could result in adverse biological responses;

— reduction of toxicity by means of reformulation or materials change;

— changes to production processes to reduce or eliminate hazardous residues or process additives.

Risk can also be controlled by providing data to allow a more accurate risk estimate than one based on worst case default assumptions. The choice of tests should be based on an initial risk analysis that identifies the uncertainties that need to be addressed and the most suitable way of addressing them. In some cases, an identified risk for which there is some uncertainty can be mitigated by means other than testing (e.g. warnings, contraindications).

If new hazards or a higher level of existing risk results from the control measures, it is possible that some retesting will be necessary.

It is emphasized that conducting animal testing for risk reduction should only be considered after all alternative courses of action (review of prior knowledge, chemical or physical characterization, *in vitro* evaluations or alternative means of mitigation) have been exhausted.

B.3.3 Evaluation of residual risk acceptability

Following risk analysis and evaluation and the implementation of risk controls, it is necessary to review the findings of these preceding activities and to document the residual risk and to decide on any further disclosure of such residual risks, for example through appropriate labelling, cautions or warnings.

B.3.4 Post production monitoring

The processes of risk assessment are based upon human judgement using the available information, supplemented by biological testing where required. This assessment should be updated as needed with new information that becomes available from post market monitoring of medical device performance and safety in actual clinical use. This monitoring should include both trends in adverse events associated with the specific medical device in question, plus new information which arises in relation

to other relevant similar medical devices or materials. Monitoring should also include ongoing review of relevant scientific literature.

B.4 Guidance on specific aspects of biological evaluation

B.4.1 Material characterization

B.4.1.1 Chemical characterization

From a practical perspective, chemical characterization data are most useful in a biological assessment when:

— issues of a proprietary nature can be resolved;

— only one or a small number of chemical constituents are changed in a medical device;

— toxicity data are readily available for the chemical constituent(s);

— extraction/analytical chemistry studies are easily conducted.

B.4.1.2 Use of chemical characterization data in a biological evaluation

There are several clauses/subclauses in this document that ask the user to conduct a chemical characterization of the medical device undergoing the biological evaluation. For example, 4.3 instructs the user to take into account the intended additives, process contaminants, residues, and leachable substances for their relevance to the overall biological evaluation of the medical device. However, as a practical matter, no specific guidance is given on how to take this information into account when performing the biological evaluation.

From a hazard identification standpoint, information on the compounds released from the medical device can be useful in selecting appropriate biological evaluation tests. For example, if a compound is known to produce nephrotoxic effects, special attention could be paid to that endpoint when conducting either acute or subchronic toxicity tests as described in ISO 10993-11. Such information can be used to focus the biological testing strategy to address the most clinically relevant endpoints.

Chemical characterization data can also be useful for risk estimation. If data are available on the rate at which a compound is released from the medical device under conditions that simulate the in-use environment, and if sufficient data are available to derive a relevant toxicological threshold or chemical specific limit (see ISO 10993-17, and ISO 10993-18), then it is possible to compare the dose received to the relevant threshold or limit in assessing likelihood of adverse effects.

B.4.1.3 Proprietary materials formulations

Where the necessary data (e.g. complete formulation data) are not available to a manufacturer because of confidentiality of proprietary information, enquiries should be made with the materials supplier as to the availability of materials biological evaluations which can be relevant to the proposed application. In some cases it is possible to manage confidentiality of proprietary formulations by means of separate lodgement by the manufacturer of biological evaluation data with an independent assessor or regulatory agency (known as a "Master File" in some jurisdictions). These data can then be referenced in a regulatory submission by the medical device manufacturer and confidentially reviewed by the relevant conformity assessment body or regulatory agency in conjunction with the medical device submission review.

B.4.1.4 Physical Characterization

For particulates and nanomaterials (when used in medical devices) physical characterization is necessary, as described for nanomaterials in ISO/TR 10993-22. In addition, in some cases physical form (e.g. geometry, particle size, porosity, surface texture) can have a substantial effect on biological

interactions with the medical device and can impact safety. In such cases it is important to consider such aspects as part of risk evaluation. If there are insufficient data available from literature or other sources to estimate risks, then it is possible that further investigations using appropriate functional models or other investigations of the effect of physical form will be necessary. Examples include:

— evaluation of geometry on blood flow and haemocompatibility;

— evaluation of porosity on tissue ingrowth;

— evaluation of release of wear particles on local and distant tissue responses;

— evaluation of surface texture (topography) on cell adhesion, phenotypic expression and growth.

B.4.1.5 Effects of manufacturing processes

It is important to consider the effect of manufacturing conditions on materials as well as the use of additives or presence of contaminants. In general, in order to be able to support biological safety, materials testing should have been carried out on materials test samples which have been processed (including sterilization if applicable) in equivalent ways to the materials included in the final medical device in question. Where there are differences in the materials processing from that used to produce test articles to generate the test data, a justification is required as to why the differences are not significant to the determination of biological safety. Particular aspects which should be considered include:

— processes which can cause either bulk or surface changes in materials properties e.g. moulding, surface treatment, welding or machining;

— intended additives or processing aids, such as catalysts, antioxidants, pigments, surface treatments, and others;

— potential process contaminants e.g. cleaning/disinfection/sterilization agents, etching agents, mould release agents, cutting fluids and particles, machine contaminants such as lubricants or residues from the manufacture of device components made from different materials;

— degradation during manufacturing and processing, clinical use and storage;

— potential process residuals of chemicals and additives.

B.4.2 Collection of existing data

Before a data gap analysis can be conducted, the extent of relevant data should be determined, including:

— toxicology data on component materials or constituent or other relevant compounds (Annex C);

— existing biological safety data on component materials or products;

— data on history of clinical use or human exposure.

B.4.3 Device testing considerations

B.4.3.1 Tiered approaches to biological testing

When it is found to be necessary to conduct additional testing to gather further data to support a risk evaluation, then a tiered approach should be taken. Testing should begin with chemical and physical characterization and *in vitro* screens. The results of the characterization and *in vitro* testing should be reviewed before proceeding to animal testing.

B.4.3.2 When to do long-term testing (chronic toxicity, reproductive toxicity, degradation and carcinogenicity studies)

The need to conduct long-term testing requires specific consideration and justification according to the application being considered.

In the following circumstances, a correctly conducted risk assessment can provide justification for not carrying out long-term testing, where the nature and extent of exposure confirms that patient is being exposed to very low levels of substances, below relevant toxicological thresholds. The following factors can contribute to a justification for not carrying out long-term testing:

— exposure quantity (i.e. total device/material mass per patient);

— time;

— bioavailability.

The following situations are likely to indicate a need for long-term testing:

— the quantity of material present and the length of exposure indicate that long-term toxicological effects could be of concern;

— constituent compounds are known to be, or considered likely to be, toxic;

— there are insufficient prior data for the material concerned (or closely similar materials) in equivalent long-term applications;

— there are specific chemical reasons, e.g. particular molecular structures of concern, which indicate particular chronic toxicological concerns;

— shorter term screens (e.g. *in vitro* genotoxicity screens), indicate potential for concern;

— there are known concerns regarding biostability for the particular class of material of interest and there are insufficient supporting data, e.g. accelerated test data from a relevant, validated model for the specific material or formulation under consideration.

It should be noted that there are some controversial test choices in the area of long-term testing and some international differences in testing requirements.

B.4.3.3 *In vitro* system pH and osmolality compensation for absorbable materials

Polymeric, metallic, or ceramic materials that are intended to be absorbed *in vivo* will release soluble components or degradation products. If the release rate of a material is sufficiently rapid, elevated concentrations of one or more of the released products could alter the pH and/or osmolality of an *in vitro* test system. Since the *in vivo* condition provides the combined presence of perfusion and carbonate equilibria, when evaluating intentionally absorbable materials it is possible that adjustment of the pH and/or osmolality of an *in vitro* test system will be necessary to maintain physiologically relevant conditions – thereby allowing evaluation for other causation and provided a scientific justification for the adjustments and the effect on the *in vitro* test system, as performed without pH or osmolality adjustment, is documented within the report. Results from both the standard assay and adjusted assay should be compared, as modifications can mask important considerations.

B.4.4 Biological safety assessment

B.4.4.1 Use of clinically relevant data for a risk assessment

If it is determined in the biological evaluation that the medical device does not have the same chemical composition, physical properties (e.g. geometry and surface properties), or body contact as an existing medical device, Figure 1 instructs the user to determine if there is sufficient justification and/or clinically relevant data (physical, chemical and biological) for a risk assessment.

A judgement on whether there are sufficient clinically relevant data for a risk assessment can be based on several factors, including whether all materials used in the medical device have a long history of safe use in the same application. Where the materials in the final medical device are chemically identical (taking into consideration both formulation and processing) to those used in existing medical devices, the nature of exposure is the same, and clinical information from targeted analyses is available for relevant biocompatibility endpoints, then a materials characterization-based approach to risk assessment can be justified to assess biological safety.

NOTE Guidance on using data on history of safe use in medical applications can be found in guidelines from ATSDR and Japan [25][27].

B.4.4.2 What constitutes "sufficient toxicology data" including dose and route relevance

Although it is possible to identify a number of chemical compounds released from a medical device in a chemical characterization scheme, it is likely that toxicity data will not be available for some compounds by the clinically relevant route of exposure.

Although methods are available to conduct a route-to-route extrapolation of dose, including PBPK modelling as described in 6.3.2.14, these approaches should be used with caution and portal-of-entry effects should be taken into consideration.

Caution is required in interpreting effects observed in tests at very high dose levels relative to the actual exposure in clinical use. Similarly, it is possible that sample concentration within an *in vitro* test system will need adjustment to ensure the test system is representative of physiological conditions, especially when assessing absorbable materials (see B.4.3.3 for guidance on pH and osmolality compensation for absorbable materials).

Various factors that should be considered to extrapolate animal experiment data to clinical use conditions are discussed in ISO 10993-17.

B.4.4.3 Determining the acceptability of the level of leachable (allowable limit) according to ISO 10993-17

As noted in ISO 10993-17, risk characterization involves a comparison of the dose of the compound received by the patient or clinician to the "safe" dose or Tolerable Intake (TI) value for that compound. If dose/TI ratio is > 1, then there is an increased likelihood for adverse effects to occur in the exposed patient. However, the dose/TI ratio should not be thought of as a "bright line" value to determine the acceptability of the level of the leachate. The greater the value of the dose/TI ratio, the greater the likelihood is of adverse effects occurring in the patient and/or user; however it is important to also take into consideration such factors as severity of adverse effects seen in the study that serves as the basis for the TI, the pharmacokinetics of the compound, the conditions used to extract the compounds from the medical device, and whether default or conservative assumptions were used to derive the TI. ISO 10993-17 includes information on the clinical use of the medical device and availability of alternative materials to derive an allowable limit (AL) and assess whether the level of a compound leached from a medical device is acceptable.

B.4.4.4 Thresholds of Toxicological Concern (TTC)

When considering the presence in a material of potentially toxic components which are present at low concentrations, and a tolerable intake (TI) cannot be derived from the literature, consideration should be given to the concept of a "threshold of toxicological concern". It is possible to establish by reference to the known toxic effects of the substance in question, in particular the toxic dose, that the substance is present in sufficiently low amounts to not present a significant risk.

B.4.4.5 Guidance on mixtures in risk assessment

ISO 10993-17 notes that patients or clinicians are rarely exposed to only one residue at a time. It is more likely that exposure occurs to multiple compounds released from the medical device. This co-exposure

to multiple compounds has the potential to increase or decrease the toxicity of a constituent of the mixture if this compound was administered alone.

Figure 1 asks the user to consider if the toxicity data for individual compounds are applicable if the patient or clinician is exposed to this compound as part of a chemical mixture. Data are rarely available on the effect of a compound as a constituent of a chemical mixture and this requirement places a very high standard on the use of toxicity data for single compounds for the biological evaluation of medical devices. If compounds are structurally similar, they could result in an additive toxicological effect. For compounds that are structurally dissimilar, it is unknown whether chemicals might have an additive or inhibitory toxicological effect. In addition, compounds could chemically interact, resulting in new chemicals that could introduce similar or new types of toxicological risks. Methods to address risk assessment of mixtures are given in Annex B of ISO 10993-17.

B.4.5 General guidance

B.4.5.1 Changes which can require re-evaluation of biological safety

Conventional medical device design practices require that a risk assessment be revisited when a design change occurs. If the design is modified, changes made on the medical device could alter the biological performance of the medical device. It is therefore important to evaluate the effect of a change. The biological risks associated with a change should be identified, evaluated, assessed and controlled. Testing should not be conducted if risks are found to be unacceptable. Otherwise additional information should be obtained. Tests should only be undertaken if they are judged likely to assist in reaching a conclusion. A rationale for testing should therefore be based on an analysis of the relevant risks from the existing data.

It is important to understand that although material changes do trigger the need for re-evaluation, the scope of that re-evaluation should be appropriate to the nature of the change and should focus on the specific materials changed, the nature and use of the medical device and the potential interactions.

If tests are considered necessary, a tiered approach should be used as for original testing. Testing should be conducted in the following sequence:

1) physical and chemical characterization;

2) *in vitro* testing;

3) animal testing.

The final animal testing step should only be carried out if the prior characterization tests and *in vitro* studies do not provide sufficient information.

Typical changes that could alter the biological performance of a material or final medical device include, but are not limited to:

— processing e.g. sterilization, cleaning, surface treatment, welding, injection moulding, machining, primary packaging;

— material source e.g. new vendor, new facility;

— material specification e.g. wider tolerances, new specification;

— formulation e.g. new materials, new additives, change in tolerances;

— storage conditions e.g. longer shelf-life, wider tolerances, new transportation conditions;

— biological environment (i.e. change in clinical use).

Properties to consider following a material change include, but are not limited to:

— chemical composition e.g. composition, purity, leachable profile;

- physical properties e.g. morphology, topography;
- mechanical properties e.g. wear resistance, strength;
- biostability, environmental stability and chemical stability;
- biological effects of electrical properties and EMC.

Chemical characterization data are used in risk assessment to judge equivalency, in toxicological terms, of a proposed material to an existing clinically established material for the same type of clinical exposure. Principles for judging toxicological equivalency are described in ISO 10993-18:2005, Annex C.

B.4.5.2 Good laboratory practice

Any testing to support a biological evaluation is expected to be an integral part of a manufacturer's quality management system and is therefore subject to the same requirements for validation and traceability as any quality control test. Assurance is needed that the conclusions about safety upon which development and marketing decisions are based are well founded. A safety assessment is only as good as the data supporting it. It is necessary therefore to verify the scientific integrity of all components of an assessment. Quality systems controls applicable to non-clinical testing are known as Good Laboratory Practice (GLP). GLP studies are carried out to defined quality standards in laboratories that are accredited in line with an internationally implemented governmental scheme. Typically studies will be conducted under a laboratory quality system compliant to ISO/IEC 17025 or an equivalent standard.

B.4.5.3 Biocompatibility evaluation documentation

Documentation for a biocompatibility evaluation should include, to the extent feasible and necessary:

- a general description or drawing of the medical device;
- quantitative information on the material composition/formulations and quantitative or qualitative information on physical characteristics for all device components with direct or indirect contact as defined in 5.2;
- description of processing conditions that could introduce manufacturing contaminants;
- a review of available toxicity and prior use data relevant to each medical device component with direct or indirect tissue contact as defined in 5.2;
- reports of biological tests;
- an assessment of the data;
- a statement confirming the risk analysis and risk controls have been completed.

The information collected should be incorporated in the medical device design documentation as part of the process of design control (for example ISO 13485:2016, Clause 7). It should also form part of the risk management file (ISO 14971:2007, 2.23). Non-clinical and clinical studies are an aspect of design verification and validation, (for example ISO 13485:2016, 7.3.6 and 7.3.7 respectively). A product design dossier compliant with ISO 13485 design controls will include clearly specified design input requirements (including requirements for biological safety) and records of non-clinical tests, clinical investigations, and design reviews that verify that the medical device as designed meets these requirements.

Annex C
(informative)

Suggested procedure for literature review

C.1 Introduction

A review and evaluation of the literature is essential for justification and planning of any biological evaluation of a material or a medical device. The aim of such a review is to determine scientific background for the biological evaluation. It also provides essential information for assessing risks/benefits and achieving the ethical conduct of the planned evaluation as required by ISO 10993-2.

NOTE Such a literature review can be helpful to assess whether the relevant data available in the literature are sufficient to demonstrate biological safety of the medical device in question without the need to generate further data from actual testing or to conclude that the available data are not sufficient.

Performing a literature review is a scientific activity that should be done with rigour and objectivity, and should allow verification by third parties.

C.2 Methodology

C.2.1 General

Prior to performing the literature review, a plan should be established for the identification, selection, collation and review of all available studies/data. This plan should be documented and based on recognized practice for systematic review of the scientific literature.

C.2.2 Objective(s)

The objective(s) of the literature review should be clearly defined. The types of study that are relevant to these objectives should be specified, taking into account any already well-established knowledge of the material or medical device.

C.2.3 Selection criteria for documents

The criteria for selecting or excluding data should be defined with an appropriate rationale. Published data should be taken from recognized scientific publications. Preference may be given to GLP over non-GLP data. All available unpublished relevant data should also be taken into account in order to avoid publication bias. All data should be referenced.

The literature review should state the sources of literature and data, and the extent of the searches of databases or other compilations of information.

C.2.4 Assessment of documents

A literature review should clearly assess the quality of the documents and the extent to which the literature relates to the specific characteristics and features of the material or medical device under consideration, taking into account the intended use of the medical device.

The following should be considered:

a) similarity of the material or medical device in the selected documents to the medical device under consideration based on technology, critical performance, design and principles of operation, so that the applicability of the literature can be assessed;

b) the relevance of the particular experimental animals used in the selected studies for the biological evaluation of the material or medical device under consideration;

c) conditions of use of the material or medical device in the selected documents and the intended use of the medical device in question.

C.2.5 Critical evaluation of the literature

The literature review should make an assessment of the significance and weight of studies of different designs and between published and unpublished data. If unpublished data are being included in the assessment, the literature review will need to identify the significance that is attached to these.

Factors include:

— whether the author's conclusions are substantiated by the available data;

— whether the literature reflects the current medical practice and state of the art technologies;

— whether references are taken from recognized scientific publications and whether or not they have been reported in peer reviewed journals;

— the extent to which the published literature is the outcome of a study/studies that have followed scientific principles.

The literature review should contain a critical evaluation of the literature. After documents are obtained and assessed, the selection criteria that are applied and the exclusion of any documents from this critical evaluation should be justified. A review is then completed as it relates to the medical device in question and its intended use, and a structured report of the review should be written, consisting of:

— a short description of the material or medical device including its intended use;

— an analysis of all the selected literature and data, both favourable and unfavourable;

— a critical evaluation of the hazards, associated risks and appropriate safety measures;

— a description of the methods of weighting the different papers; particular attention should be given to circumstances where there are repeated publications by the same authors, in order to avoid over-weighting multiple publications of the same tests;

— a list of publications appropriately cross-referenced in the evaluation;

— a conclusion with a justification, making it clear how the objectives of the literature review have been met and how any gaps in the evidence necessary to cover all relevant aspects of safety and performance have been identified;

— the signature(s) of the reviewer(s) and date.

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